COMMENTARY

Whither *Mycobacterium vaccae*—encore

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Reichman,[1] commenting on the results of a randomised controlled trial in South Africa in which the efficacy of *Mycobacterium vaccae* immunotherapy was studied in patients newly diagnosed with tuberculosis,[2] said that "The conclusion, from the Durban Immunotherapy Trial Group . . . is inescapable—*M vaccae* has virtually no effect, positive or negative, on tuberculosis." This conclusion was challenged[3] as being premature because of a flaw in the trial in that only one dose of *M vaccae* was given.

In studies of the immunological effects of *M vaccae* on patients with cancer, repeated vaccination was required to induce a change in the cytokine pattern to that of a Th1 (cell-mediated) response. The hypothesis underlying the use of adjunctive *M vaccae* in tuberculosis treatment is that entrenched Th2 (humoral) dominant responses in the lung lead to inflammation, necrosis, and cavitation. *M vaccae* is believed to promote Th1 responses important to host defences against intracellular pathogens and restore recognition by the host of shared mycobacterial antigens.[4] The investigators in the Durban study acknowledged the need for looking at multiple doses, but rejected the charge of inadequate design in their study because it was based on the available information at the time.[5] They also pointed out that the potential to drive a predominant type-1 response in advanced multicavitatory tuberculosis might not equate to faster sputum conversion, ie, the point at which tubercle bacilli cannot be cultured. With ordinary chemotherapy based on rifampicin, isoniazid, pyrazinamide and ethambutol, all patients demonstrate sputum conversion between two and three months after initiation of therapy. Generally, the earlier sputum conversion occurs, the more bactericidal a treatment regimen is considered to be, therefore serving as a useful marker of clinical efficacy and of eventual cure of the patient.

In this issue of *The Lancet*, Alwyn Mwinga and colleagues present further results with a single injection of *M vaccae* (SRL172) in tuberculosis patients. Their trial is different from the Durban trial in two main respects—it was done in HIV-seropositive tuberculosis patients and the primary outcome measure was mortality. There was no evidence that *M vaccae* has any significant effect on survival. But it would be too easy to reject *M vaccae* as an agent with a role in the treatment or prevention of tuberculosis. Further investigations continue and reports of proposed efficacy periodically appear, keeping the controversy alive.

In the recently held 4th World Congress on TB, Wu and colleagues[6] presented data from animal and human studies in which multiple doses of *M vaccae* were used. Lung lesions were not observed in the mice treated with *M vaccae* at month 5 after immunotherapy. 77 newly diagnosed patients on commonly used rifampicin-based short-course chemotherapy were randomised to receive saline placebo or *M vaccae* three times every 2 weeks after start of drug therapy. Sputum conversion after a month of tuberculosis treatment occurred more frequently among patients receiving *M vaccae* but was similar at later months to controls. A similar observation was made in an earlier study in Uganda with a single injection of *M vaccae*,[7] and Mwinga and colleagues mention the possibility that the 2-month sputum conversion data in their study might indicate that an early effect of sputum conversion may have been missed (1-month sputums were not collected). Increased sputum conversion at 1 month in the Uganda study was associated with greater improvement in chest radiographs at the end of chemotherapy. Further, *M vaccae* administration was not associated with modulation of the production of cytokines, including interferon-γ and tumour necrosis factor-α.

Several other studies on *M vaccae* in newly diagnosed tuberculosis patients and also on multidrug-resistant patients come from China. One of these[8] attempted to demonstrate the effect of *M vaccae* in a treatment-shortening trial, and compared treatment with 4 months of antituberculosis drugs plus multiple doses of *M vaccae* for 6 months with standard 6-month chemotherapy. Sputum conversion after 1 and 2 months was significantly greater in the group receiving *M vaccae*. Relapse rates after treatment were low and did not differ (3% *M vaccae vs* 5·6% placebo).

The attention to *M vaccae* has begun to shift to an investigation of its role in cancer therapy, where it is reported to be showing promise,[9–11] and in multidrug-resistant tuberculosis. In a randomised trial from China,[12] sputum conversion, cavity closure, and relapse were significantly better in patients with MDR TB treated with *M vaccae* every 3–4 weeks for 6 months plus susceptibility-directed chemotherapy compared with those on chemotherapy alone.

In view of the many studies with *M vaccae* over the past 10 years at least, and the conflicting results from studies with sometimes closely similar designs, the question of the validity of such trials necessarily arises. De Bruyn and Garner[13] did a Cochrane review of studies in which the effects of *M vaccae* as an adjunct to chemotherapy for treating tuberculosis were investigated. Up to the year 2000 they identified only six trials for inclusion in their review. The main findings were that *M vaccae* had no effect on mortality and no consistent effect on sputum negativity or sputum culture. They concluded that immunotherapy with *M vaccae* does not benefit patients with tuberculosis.

The last word on *M vaccae* and its potential role in tuberculosis control has not been spoken. What is the way forward? Properly designed clinical trials have not shown efficacy. On the other hand, some studies suggest activity for clinical, radiological, and laboratory endpoints. Future trials must incorporate dose-ranging with the best available correlate of protection—whole-blood production of interferon-γ—to provide a rationale for selection of the dose and schedule for administration.

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Cigarette smoking and risk of breast cancer in women

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Breast cancer is the most frequently diagnosed cancer in women from all ethnic groups.[1,2] In 2002 the number of newly diagnosed invasive breast cancers in the USA is expected to increase by about 6% from the previous year, reaching an approximate total of 203 500 cases.[1,2] Similar trends are observed worldwide, even in countries with a low incidence of breast cancer.[3,4] Breast cancer was the leading cancer cause of death in women until 1987, when it became second to lung cancer.[5] Tobacco smoking is recognised as a major health risk in women.[5,6] Among the many diseases caused by smoking cigarettes, lung cancer is foremost, with 79 200 new cases, and 65 700 lung-cancer deaths in the USA this year alone.[2] The incidence of lung cancer in women has increased from six per 100 000 in the early 1960s to 28 per 100 000 in 1987, in parallel with the increase in the percentage of women in the USA smoking cigarettes; from 32·8% in 1959 to 43·6% in 1982.[7] Although by 1998 the percentage of smokers had dropped to 22% for all women and to 30% for high-school senior girls,[5] lung cancer mortality in women has increased seven to eightfold between 1950 and 1998.[8]

The clear association between tobacco smoking and lung cancer has led researchers to postulate that cigarette smoking could represent a risk factor for breast cancer.[5] This hypothesis is supported by experimental evidence that the carcinogen benz(a)pyrene, present in tobacco smoke, induces neoplastic transformation of human breast epithelial cells.[9] However, this association remains controversial,[10] mainly because breast cancer is hormone-dependent, and evidence indicates that cigarette smoking has an antioestrogenic effect in women.[11]

In an article in today's *Lancet*, Pierre Band and colleagues have carefully evaluated conflicting epidemiological data and experimental preclinical data in designing a population-based case-control study that allowed the investigators to uncover a dual action of cigarette smoke on the breast. The investigators test the hypothesis that cigarette smoke exerts competing effects on breast-cancer risk. Preclinical data have demonstrated that carcinogens are capable of inducing malignancies when they affect the undifferentiated and highly proliferating mammary epithelium of young nulliparous females, but fail to induce cancer when the exposure occurs after the mammary epithelium has become either differentiated (ie, after pregnancy and lactation), or quiescent after the menopause.[9] The application of this paradigm to the investigators' working hypothesis requires two major assumptions: first that breast cancer diagnosed in younger women was initiated by cigarette exposure during puberty or at least before a full term pregnancy, and second that breast cancer diagnosed in older women (postmenopausal group) was initiated at a much later period, probably during the perimenopausal period and after completion of all reproductive events, when the breast was less susceptible to undergo malignant transformation.[9] A third possibility that needs to be entertained is whether women that smoked during puberty and did not develop cancer or whose cancers were diagnosed after the menopause, lacked specific enzymes for activating tobacco carcinogens, and therefore benefited from the antioestrogenic effects of tobacco. Although much work needs to be done to prove these postulates, the hypothesis has been cleverly explored through the design of Band's study, which addresses the influence of age at diagnosis, and therefore menopausal status, on the response of the breast to cigarette smoke exposure.

Band and colleagues found that in premenopausal women, the risk of breast cancer was increased both in parous women who started to smoke within 5 years of menarche and in nulliparous women who smoked 20 cigarettes or more daily for 20 or more cumulative pack–years. Postmenopausal women whose body-mass index increased from age 18 and who started to smoke after a first full-term pregnancy had a significantly reduced risk of breast cancer. This finding is of great interest, since women older than 55 are the only group in which an increase in body mass of 10 kg has been associated with 7% increase in breast cancer risk, an effect not observed in younger women.[12] These findings suggest that in older women the antioestrogenic effects of smoking may modulate the increased risk seen with an increase in body mass index alone.

There is increasing evidence that the association between breast cancer and established risk factors is

greatly dependent on the age of the woman at the time of diagnosis of the disease.[12] It would be of great interest to investigate whether smoking, either active or passive, influences breast cancer risk differently in those women diagnosed before the age of 40 years in comparison with perimenopausal (diagnosed between 40 and 55), or postmenopausal (diagnosed after 55) women, as defined by Tryggvadóttir et al.[12] The findings of such a study might provide a mechanistic explanation for the increased breast cancer risk observed by Band and colleagues in both parous and nulliparous premenopausal women who smoke, since breast cancer in very young patients seems to be influenced to a greater degree by events affecting the breast during the puberty.

Epidemiological studies designed to take into consideration age at diagnosis and age at exposure to risk in relation to parity history would provide vital information on the factors that influence cancer initiation. The disparity in the observed effect of risk factors in premenopausal and postmenopausal women would probably persist or might even be enhanced in women diagnosed at a very young age. Future studies should be able to clarify whether breast cancer diagnosed in very young women is a disease that differs in its aetiology or mechanisms of initiation and progression from that diagnosed at perimenopause or post-menopause, or whether age at diagnosis is an indicator of variations in susceptibility to carcinogens at the time of initiation or identifies cases with an earlier onset. Future epidemiological studies will certainly take advantage of advances in the understanding of the pathogenesis and molecular biology of breast cancer to unravel the role of genetic predisposition, endocrine and reproductive factors, and environmental exposures on the initiation of cancer.

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Biomedical science matters for people—so its impact should be better assessed

"From bench to bedside" epitomises the interdependence of biomedical research and clinical care: scientific developments pave the way for innovations in prevention, diagnosis, and treatment of diseases. Given that funding bodies, policy makers, and in all probability the public are likely to want as much return as possible from their investment in research, the best proposals for studies should be allocated to the most accomplished research team(s). Regular review of the quality of research programmes has become routine in many countries and is usually based on international journals' impact factors, but the use of impact factors to measure "success" has been questioned.[1] The extent to which research influences clinical practice and the impact research has on patients' well-being—intuitively relevant aspects—are not taken into account.

For that reason a recent report by the Royal Netherlands Academy of Arts and Sciences[2] is relevant. *The societal impact of applied health research—towards a quality assessment system* seeks to broaden the criteria for assessing the impact of research on society. The report presents a comprehensive list of indicators of research quality, presentation to medical and other professions, and inclusion in guidelines, protocols and the teaching of health-care professionals (panel). The criteria highlight interactions between researchers and stakeholders of all interests. The societal implications of biomedical research particularly concern primary care and the report was spurred by experiences in fields such as general practice, epidemiology, technology assessment, and quality assurance. But, being directed at applied health-care research, the scope of the report is broader than its use to assess the quality of research.

The demand for research funding has long exceeded the available budget, which is why selection is needed. Increasingly demanding review systems have been set up to identify and fund the best proposals. Rigorous review has improved biomedical science, but investments in research are broader than just the allocation of money for research projects. Research requires an infrastructure—from laboratory facilities to access to patient-related data, from the expertise of research staff to the career prospects of young researchers—and a direct link to patients' care. Insight into the main challenges for the practitioner, into the limitations and adverse effects of current practice, and into the relative impact of previous research, are important tools to steer research into areas such that clinical care is not entirely dependent on scientific serendipity.

A reason to include other than scientific criteria when assessing research outcomes comes from the relation between biomedical research and patients' care. This relation is not straightforward and research as such is no guarantee that better care will result: despite the availability of new information, practitioners' persistence with established routines is notorious.[3] On the other hand, in striving to keep up-to-date, practitioners feel overburdened by the amount of new research findings. It is important to identify the "good and relevant". Systematic reviews that take into account scientific rigour go some way towards addressing this problem. Inclusion of studies in a systematic review or research groups' participation in systematic reviews should be considered a yardstick of scientific relevance, in particular in relation to the Cochrane Collaboration,[4] as the Dutch report[2] concurs.

Also needed are studies on the introduction of innovations, on their effectiveness in real practice, and on the change to clinical routines. Such studies are now part of the research field, with research groups, a research audience,

Criteria and indicators of societal impact of research output[2]

Criterion	Indicator
Content analysis	Professional publications
	Treatment guidelines and protocols
	Policy documents
	Cochrane library
	Textbooks
	Teaching material
	Lay publications
	IT and software (internet/CD)
Citation analysis	Scientific publications
Authorship	Authorship mentioned under content analysis
Products	Health-care technologies and services
	Instruments, programmes, methods for (assessment or implementation of) care
Funding of research	(Semi) governmental funding
Publicity	Presentations for non-scientific audience
	Fact sheets
	Mass media
	Internet
Memberships	Member of committee for policy document or guideline
	Member of advisory committee
Teaching	Research-output-based contributions to education of health-care professionals
Implementation strategy	Membership of advisory committees
	Interaction between researchers and public administrators
	Feedback from target groups
Independence	Operationalisation of research questions
	Research methodology
	Analysis and publication of research

and journals of their own. Particularly when it comes to the transfer of science to practice, publication in internationally esteemed journals may not be the most important. National or regional journals, possibly in local languages, might be a better medium for the transfer of research findings, as might methods other than journal publication. Contributions to protocols and guidelines, to postgraduate education programmes, or to websites might reflect better what patients, and society at large, get back from some studies. The report[2] makes a strong case to start measuring these contributions and recommends universities and research institutes to include the criteria and indicators from 2003 onwards. In preparation, pilot reviews are suggested and incentives should be granted on the basis of societal impact and scientific quality.

Societal markers of research must be considered with, not instead of, an analysis of impact based on published papers. The first criterion in the panel—content analysis—includes professional publications. In other words, the place of international publications in peer-reviewed journals of the highest quality for the respective research field remains important. Such analyses remain the best available, even in primary care. But this conclusion also emphasises the need to make the analyses better suited to measure the real scientific impact of primary care. At the moment primary care is under-represented in MEDLINE, because the inclusion of new disciplines, such as primary-care research, necessarily lags behind more established disciplines.

The broader implications of the report[2] lie in clarifying the social impact of biomedical research, and in helping biomedical scientists to explain better to the outside world the relevance of their work. Knowing more about social impact would offer a platform to discuss the implications and contributions of biomedical research for the care of patients with the non-scientific community, and with politicians, funding bodies, patients, and medical professional organisations. Such communication would offer—in the traditionally closed-shop of the research community—transparency showing where limited resources have been spent and with what results.

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Environmental stewardship and drugs as pollutants

It is early morning—do you know where your drugs are? More than likely, some are on their way to local streams, rivers, and perhaps even farms, as sewage biosolids used as fertiliser. The public's inseparable connection to the environment is illustrated by an emerging understanding of drugs as environmental pollutants. That any chemical introduced commercially has the potential to find its way into the environment is not surprising, but pharmaceuticals and personal-care products as environmental pollutants have captured the attention of the public and the mass media because such pollutants result not primarily from manufacturing but from widespread and continual use in human and veterinary clinical practice.

Beginning in the 1970s, an escalation of research and monitoring, mostly by analytical chemists, has revealed the propensity for drugs and metabolites to enter the environment—usually by treated and untreated sewage. Many drugs from a wide array of therapeutic classes have been established as ever-present trace environmental pollutants in surface and ground waters,[1–5] generally occurring at concentrations (eg, ng/L–µg/L) far below human therapeutic levels. Although drugs, by contrast with most conventional (regulated) pollutants, are usually nonvolatile, they can also end up on the land by the disposal of sewage biosolids. Also, and again by contrast with most regulated pollutants, which have longer environmental half-lives, the continual environmental introduction of drugs by sewage effluent makes them "pseudopersistent" pollutants with ramifications for aquatic organisms. The precautionary principle, given the worldwide importance of freshwater resources, underscores the need to minimise any impacts on water supplies (eg, treatment of wastewater for reintroduction and storage in groundwater drinking supplies) and resultant potential for human or ecological cumulative exposure.

The many facets of this complex issue are captured in several reviews[1–5] and on the US Environmental Protection Agency's web site.[6] The most comprehensive environmental

monitoring-project is being published in stages by the US Geological Survey.[7] For risk assessment, published work (almost exclusively in the non-medical literature) has focused predominantly on environmental origins and sources and on occurrence,[1–5,7] and more recently on treatment-processes for waste and drinking water. Much less is known, however, about human and ecological exposure, and less yet about the known or potential hazards associated with multiple exposure to these synthetic substances, many of which are highly bioactive (eg, 17α-ethinyloestradiol).[2,4]

Regardless of whether drugs and personal-care products as environmental pollutants eventually prove to pose ecological or human-health risks, there are three major but still largely unrecognised reasons—unrelated to the molecules themselves—for developing means of reducing their introduction to the environment. By taking various actions to reduce the purposeful (eg, disposal of unused drugs via toilets) and inadvertent (mostly by excretion) release of such compounds, significant collateral benefits could arise for people as well as for their environment.

First, any improvement in technology for the removal of trace levels of drugs from waste and drinking water will more than likely also remove other unregulated pollutants, many of which have yet to be identified and others of which will come from new commercial chemicals. Thomas Ternes and colleagues[8] recently demonstrated that simple treatments, such as ozone oxidation or activated-carbon adsorption, albeit techniques not widely used, can efficiently remove drugs from drinking water. However, oxidative treatments (ozonation as well as chlorination and ultraviolet irradiation) can create many daughter products from parent chemicals; true mineralisation can be difficult to achieve. Other oxidative processes, such as ultraviolet irradiation, or physical removal, such as membrane filtration, used simultaneously or sequentially, should remove drugs and other xenobiotics.

Second, any efforts at pollution prevention (source reduction, minimisation, elimination[2,6]), most of which would originate from a broad range of sectors in the health-care industry, could have significant consequences for improved consumer-health and reduced health-care spending. Third, the risks (if any) posed by drugs as environmental pollutants must be considered only as part of the larger risk-puzzle. Organisms are rarely ever exposed to just one toxicant at a time. Their vulnerability (or tolerance) is a multidimensional function of many variables throughout the duration of exposure to anthropogenic and naturally occurring toxicants. Any adverse effect is a function of not just current exposure but also combined exposure history. An organism's tolerance depends on the duration of exposure to many chemical (and non-chemical) stressors, many of which share the same mechanism of action and whose effects can therefore at least be additive. Indeed, recent work is beginning to better show the significance of exposure to mixtures of chemical stressors at low concentrations. Nissanka Rajapakse and colleagues[9] showed that a mixture of 11 xeno-oestrogens, where each was below its no-observed-effect level, significantly increased the action of 17β-oestradiol in the yeast oestrogen-screen.

Reaching a rational assessment of the risks posed by drugs as environmental pollutants needs to be done with a minimum investment of resources, which means avoiding reinvention and rediscovery. The synthesis of reports that span many fields has a key role,[6] as does the critical need for collaboration between the traditionally separated environmental and medical sciences. Almost nothing has been published in the medical literature with the stated objective of determining the causes, extent, risks, or solutions to the issue of drugs as pollutants.[10] Collaborations among the environmental and medical sciences are important because in the final analysis, human health and the "health of ecology" are intimately tied, and in many respects, indistinguishable.

CGD's views do not necessarily reflect the views and policies of the US Environmental Protection Agency.

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Remarkable lives, remarkable words

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Many enjoy reading about the lives of remarkable people; John Aubrey's *Brief Lives*, James Boswell's *A Life of Johnson*, and Lytton Strachey's *Eminent Victorians* still delight a wide readership. Often it is through an account of a person's life and work—with all its contradictions, ambiguities, achievements, and sometimes scandals—that we can learn about the past or understand the present. As Ralph Waldo Emerson somewhat provocatively remarked, "There is properly no history; only biography". The obituary, a condensed form of biography, is perhaps the most immediate and accessible way to celebrate a life. This week we reinstate our obituary page after a lengthy absence. We intend it to be an occasional feature, commemorating the life of remarkable individuals who are internationally renowned for their contribution to medicine. We welcome suggestions from readers.

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